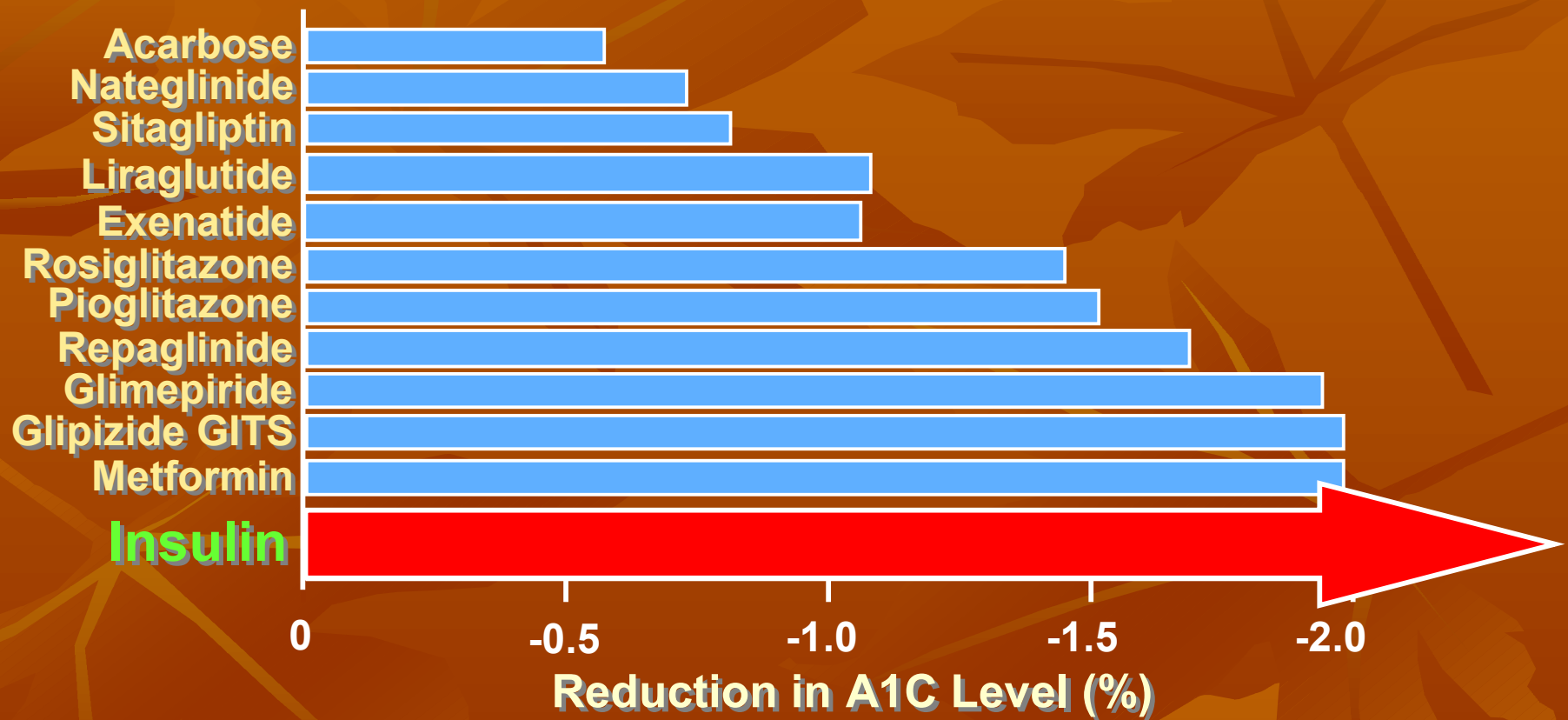# Insulin Initiation and Intensification

Elizabeth H. Holt, MD, FACE

Why Insulin Therapy in Diabetes?

- Greatest potency of <u>all</u> available therapies
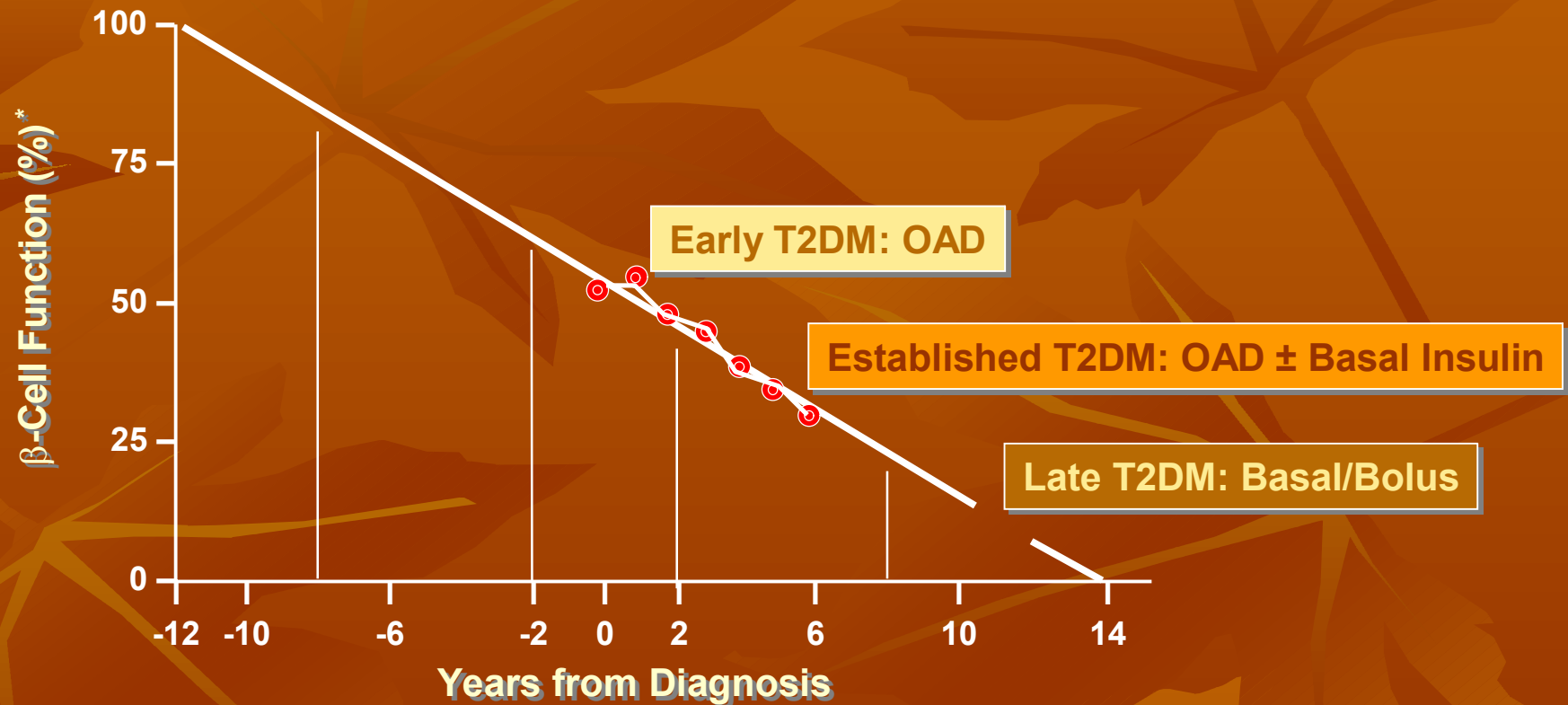- Central role in both Type 1 and Type 2 Diabetes

Insulin Deficiency (Absolute)

Insulin Resistance

+

Insulin Deficiency (Relative)

Type 1 Diabetes

Type 2 Diabetes

Antihyperglycemic *Monotherapy:* Maximum Therapeutic Effect on A1C

Horizontal bar chart titled "Reduction in A1C Level (%)" with x-axis from 0 to -2.0.

- Acarbose
- Nateglinide
- Sitagliptin
- Liraglutide
- Exenatide
- Rosiglitazone
- Pioglitazone
- Repaglinide
- Glimepiride
- Glipizide GITS
- Metformin
- Insulin

Reduction in A1C Level (%)

Precose [PI]. West Haven, CT: Bayer; 2003; Aronoff S, et al. *Diabetes Care.* 2000;23:1605. 1611; Garber AJ, et al. *Am J Med.* 1997;102:491. 497; Goldberg RB, et al. *Diabetes Care.* 1996;19:849. 856; Hanefeld M, et al. *Diabetes Care.* 2000;23:202. 207; Lebovitz HE, et al.
J Clin Endocrinol Metab. 2001;86:280. 288; Simonson DC, et al. *Diabetes Care.* 1997;20:597. 606; Wolfenbuttel BH, van Haeften TW. *Drugs.* 1995;50:263. 288; Nelson P, et al. *Diabetes Technol Ther.* 2007;9:317. 326. Garber AJ, et al. American Diabetes Association. 2008; 07. LB.

UKPDS: β-Cell Loss Over Time

β-Cell Function (%) *

100

75

50

25

0

-12 -10   -6   -2   0   2   6   10   14

Years from Diagnosis

Early T2DM: OAD

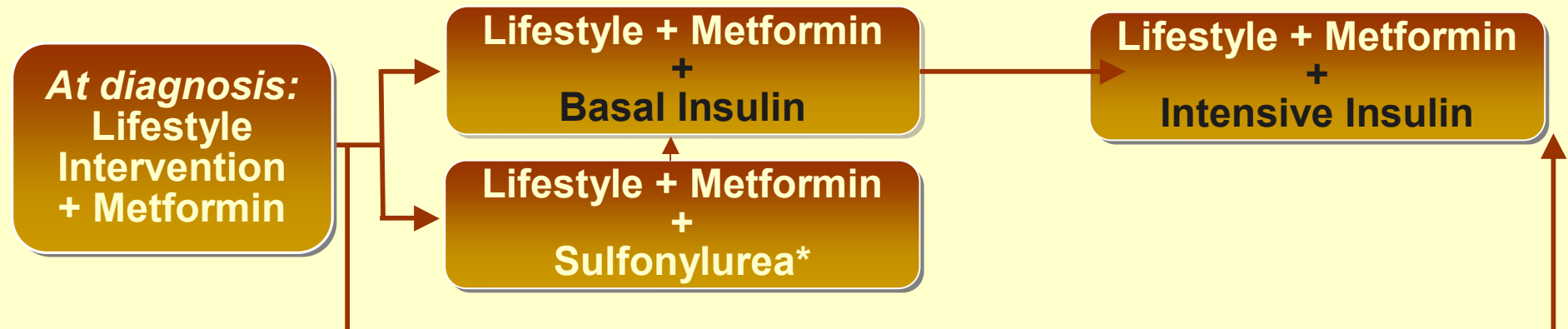**Established T2DM: OAD ± Basal Insulin**

Late T2DM: Basal/Bolus

* Dashed line shows extrapolation forward and backward from years 0 to 6 from diagnosis based on Homeostasis Model Assessment (HOMA) data from UKPDS. ʳ The data points for the time of diagnosis (0) and the subsequent 6 years are taken from the obese subset of the UKPDS population and were determined by the HOMA model.

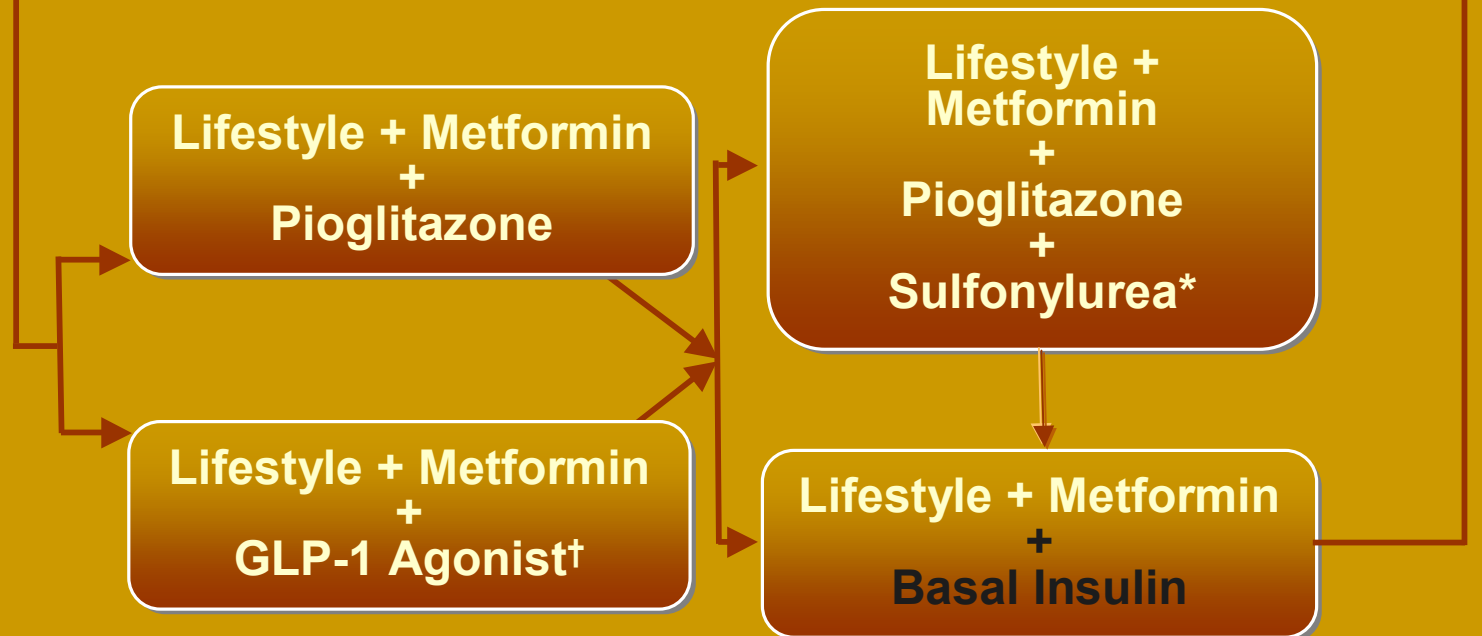Lebovitz HE. *Diabetes Rev.* 1999;7:139-153.

ADA Treatment Algorithm for Type 2 Diabetes

Tier 1: Well-validated core therapies

At diagnosis: **Lifestyle Intervention + Metformin**

Lifestyle + Metformin + Basal Insulin

Lifestyle + Metformin + Sulfonylurea*

Lifestyle + Metformin + Intensive Insulin

Tier 2: Less well-validated therapies

Lifestyle + Metformin + Pioglitazone

Lifestyle + Metformin + GLP-1 Agonist†

Lifestyle + Metformin + Pioglitazone + Sulfonylurea*

Lifestyle + Metformin + Basal Insulin

* Excludes glyburide or chlorpropamide
« Insufficient clinical use to be confident regarding safety

CHF = congestive heart failure; GLP-1 = glucagon-like peptide 1.
Nathan, et al. *Diabetes Care.* 2009;32:193-203.

AACE/ACE DIABETES ALGORITHM *For Glycemic Control*

A1C Goal ≤ 6.5%*

LIFESTYLE MODIFICATION

A1C 6.5 – 7.5%**

Monotherapy:

MET	TZD [2]	DPP4 [1]	AGI [3]

↓ *2 - 3 Mos.****

Dual Therapy

MET	+	GLP-1 or DPP4 [1]
		TZD [2]
		Glinide or SU [5]
TZD	+	GLP-1 or DPP4 [1]
MET	+	Colesevelam
		AGI [3]

↓ *2 - 3 Mos.****

Triple Therapy

| MET + GLP-1 or DPP4 [1] | + | TZD [2] |
| | | Glinide or SU [4,7] |

↓ *2 - 3 Mos.****

| INSULIN ± Other Agent(s) [6] |

A1C 7.6 – 9.0%

Dual Therapy [8]

| MET | + | GLP-1 or DPP4 [1] or TZD [2] |
| | | SU or Glinide [4,5] |

↓ *2 - 3 Mos.****

Triple Therapy [9]

MET	+	GLP-1 or DPP4 [1]	+ TZD [2]
		GLP-1 or DPP4 [1]	+ SU [7]
		TZD [2]	

↓ *2 - 3 Mos.****

| INSULIN ± Other Agent(s) [6] |

A1C > 9.0%

Drug Naive / *Under Treatment*

Symptoms / *No Symptoms*

| INSULIN ± Other Agent(s) [6] |

MET	+	GLP-1 or DPP4 [1]	± SU [7]
		TZD [2]	
		GLP-1 or DPP4 [1]	± TZD [2]

| INSULIN ± Other Agent(s) [6] |

---

* May not be appropriate for all patients

* May not be appropriate for all patients

** For patients with diabetes and A1C <6.5%, pharmacologic Rx may be considered

*** If A1C goal not achieved safely

1. DPP4 if ↑PPG and ↑FPG or GLP-1 if ↑↑PPG

2. TZD if metabolic syndrome and/or nonalcoholic fatty liver disease (NAFLD)

3. AGI if ↑PPG

4. Glinide if ↑PPG or SU if ↑FPG

5. Low-dose secretagogue recommended

6. a) Discontinue insulin secretagogue with multidose insulin
   b) Can use pramlintide with prandial insulin

7. Decrease secretagogue by 50% when added to GLP-1 or DPP-4

8. If A1C < 8.5%, combination Rx with agents that cause hypoglycemia should be used with caution

9. If A1C > 8.5%, in patients on Dual Therapy, insulin should be considered

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So, why don't we use insulin more often?

10 Reasons Patients Avoid Insulin

1. Lack of knowledge that insulin will improve control
2. Cultural taboos and family beliefs
3. Fear of needles or injection pain
4. Fear of hypoglycemia
5. Fear of weight gain
6. Inconvenience
7. Diabetes seen as worse or more serious
8. Personal failure
9. Insulin causes complications
10. Insulin will take over my life: constant demands and decision-making

Peragallo V. *Diabetes Educ.* 2007;33:60S. 65S.

10 Reasons HCP's Avoid Insulin

1. Patients will not accept injections
2. Patients are afraid of insulin
3. Initiation of insulin is difficult
4. Risk of hypoglycemia, especially in the elderly
5. Risk of weight gain, especially in the obese
6. Patients will not take insulin correctly
7. Patients will regard insulin as a personal failure
8. Patients will not be satisfied with their therapy
9. Increasing insulin levels increases CVD risk
10. Increasing insulin levels increases insulin resistance

Hayes RP, Int J Clin Pract. 2008 June; 62(6): 8606868.

Physiologic Insulin Secretion
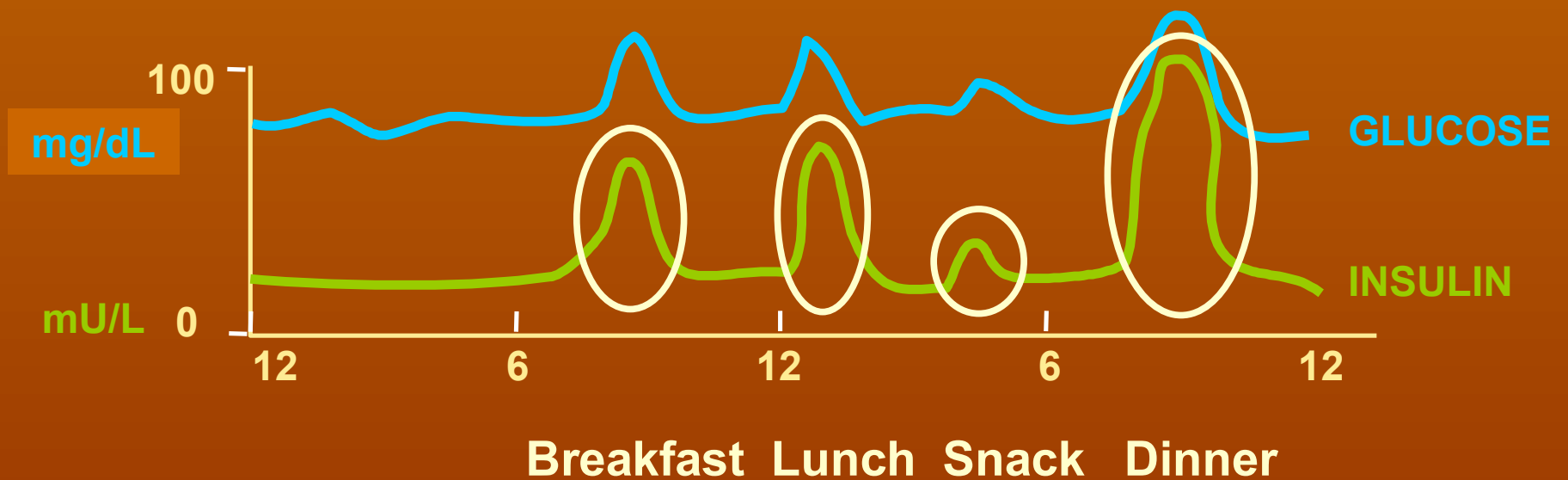
Insulin Profiles
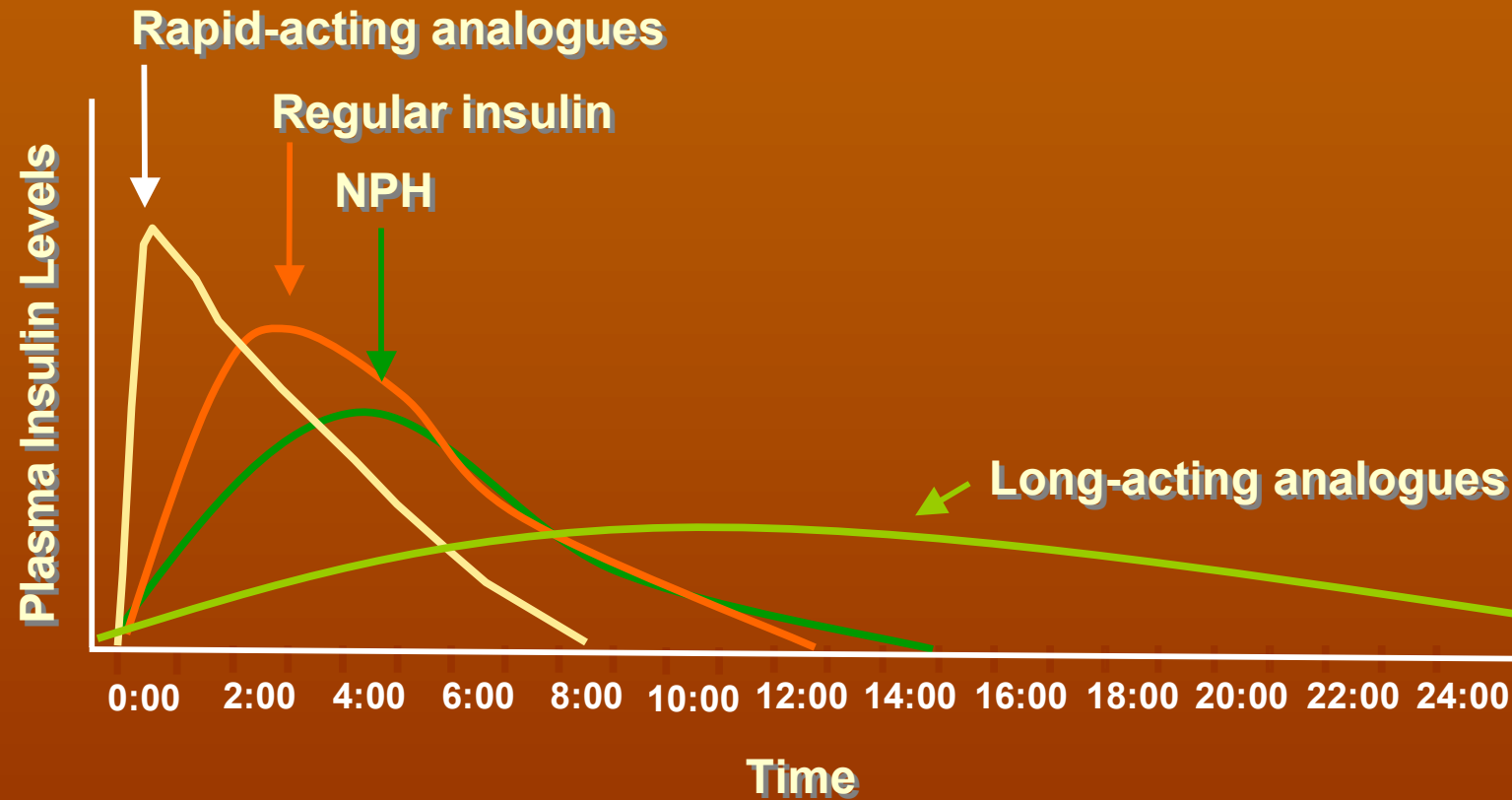
Klein O, et al. *Diabetes Obes Metab*. 2007;9(3):290-9.
Plank J, et al. *Diabetes Care*. 2005;28:1107. 1112.
Rave K, et al. *Diabetes Care*. 2005;28:1077. 1082.

Comparison of Available Insulins
(Per Prescribing Information)

Type	Onset	Peak	Duration
Short-acting			
Regular insulin (R)	30–60 min	2–5 hrs	5–8 hrs
Rapid-acting	15–30 min	30–90 min	3–5 hrs
Insulin lispro (Humalog)	10–20 min	40–50 min	3–5 hrs
Insulin aspart (Novolog)	20–30 min	30–90 min	1–2.5 hrs
Insulin glulisine (Apidra)			
Intermediate-acting	1–2 hrs	4–12 hrs	18–24 hrs
NPH			
Long-acting	1–1.5 hrs	No pronounced peak	20–24 hrs
Insulin glargine (Lantus)	1–2 hrs	Relatively flat	up to 24 hrs
Insulin detemir (Levemir)			
Premixed Insulins			
Regular/NPH insulin 70/30	30 min	2–12 hrs	14–24 hrs
Lispro protamine 75/25, 50/50	15 min	0.5–2.5 hrs	16–20 hrs
Biphasic insulin aspart 70/30	10–20 min	1–4 hrs	up to 24 hrs

John

- 62-yr old male, type 2 diabetes, diagnosed 10 yrs ago
    - BMI 30
- Current therapy:
    - Baby ASA, ACEI, statin
    - Metformin 1g twice a day
    - Glimepiride 4 mg daily
    - Sitagliptin 100mg daily
- Current A1C = 9.4%
- Home glucose ranges
    - FPG = 180-200 mg/dl
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- ROS positive for polydipsia and nocturia 3 x per night

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Triple Therapy

MET + GLP-1 or DPP4 [1]	+	TZD [2]
		Glinide or SU [4,7]

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INSULIN ± Other Agent(s) [6]

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INSULIN ± Other Agent(s) [6]

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*** If A1C goal not achieved safely

1. DPP4 if ↑ PPG and ↑ FPG or GLP-1 if ↑↑ PPG
2. TZD if metabolic syndrome and/or nonalcoholic fatty liver disease (NAFLD)
3. AGI if ↑ PPG
4. Glinide if ↑ PPG or SU if ↑ FPG
5. Low-dose secretagogue recommended
6. a) Discontinue insulin secretagogue with multidose insulin
   b) Can use pramlintide with prandial insulin
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Insulin Therapy in Type 2 Diabetes: Current Strategies

- Basal insulin therapy
  - Long-acting insulin analog once daily
  - NPH at bedtime (less desirable)
- Analog insulin (prandial or premixed) -- Human Regular Insulin is less desirable
  - Once daily at dinner
  - Twice daily (breakfast and dinner)
  - Three times daily (with each meal)
- Intensive insulin therapy
  - Basal + rapid-acting analog insulin
  - Rapid-acting or short-acting insulin delivered:
    - Once daily at largest meal
    - Twice daily
    - Three times daily (with each meal)
- Insulin pump therapy

AACE 2009 Glycemic Control Algorithm

• Rapid-acting insulin analogues are superior to regular human insulin – safer alternative

• NPH insulin is not recommended – superseded by synthetic analogues, insulin glargine and insulin detemir, which provide a relatively peakless profile and yield better reproducibility and consistency, with a corresponding reduction in the risk of hypoglycemia.

Long-Acting Insulin Analogues vs NPH in Type 2 Diabetes: A Meta-Analysis

- Provide comparable glycemic control to NPH

- Reduced risks of nocturnal and symptomatic hypoglycemia

- May be associated with less weight gain than NPH

Monami M, et al. *Diabetes Res Clin Pract*. 2008;81:184-9.

Symptomatic Hypoglycemia by Time of Day
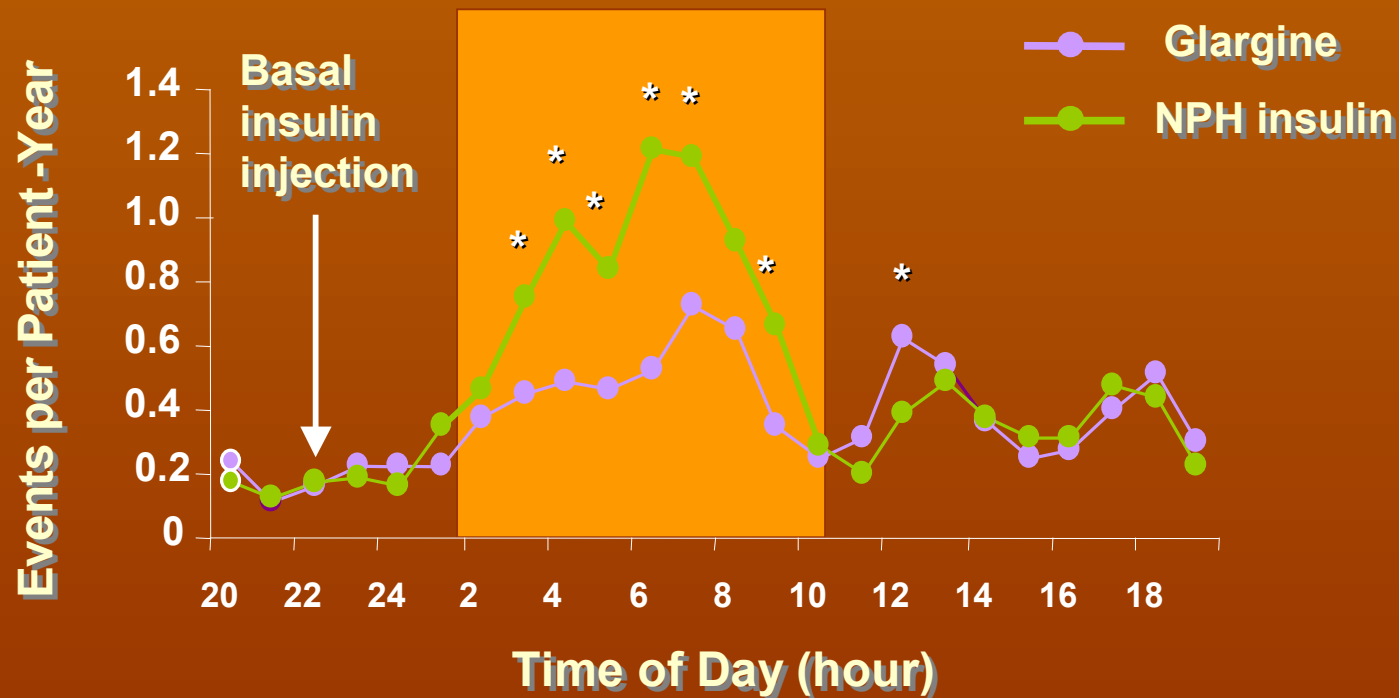
Hypoglycemia defined as PG $\leq$ 72 mg/dL, by hour

*P < 0.05 vs glargine.

Riddle MC et al. *Diabetes Care*. 2003;26:3080-3086.

Risk of Hypoglycemia with Detemir

Hermansen K et al. *Diabetes Care.* 2006;29:1269-1274.
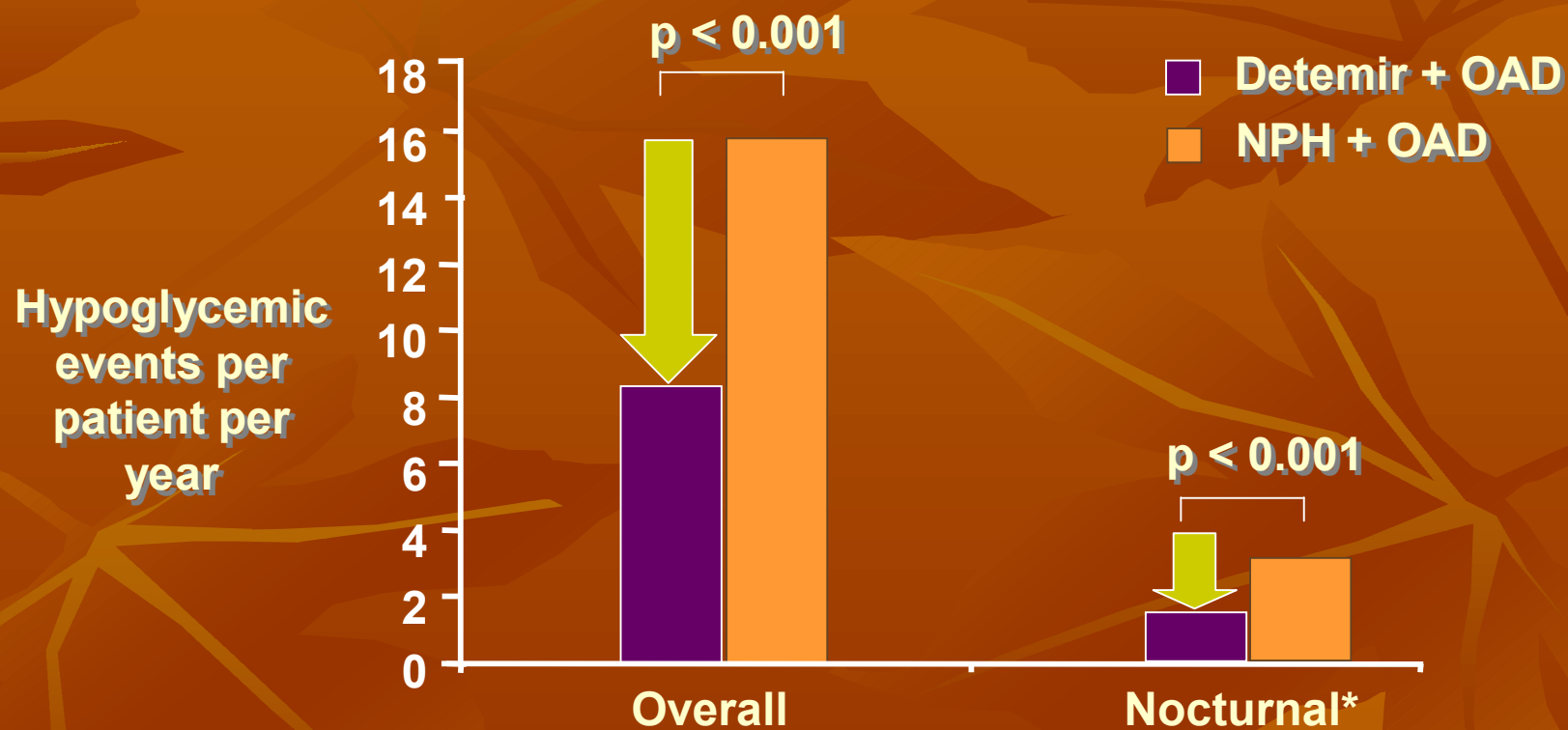
Similar Time-Action Profiles in Subjects With Type 2 Diabetes

Mean GIR profiles (smoothed with a local regression technique) for 0.4 and 0.8 U/kg detemir and glargine*
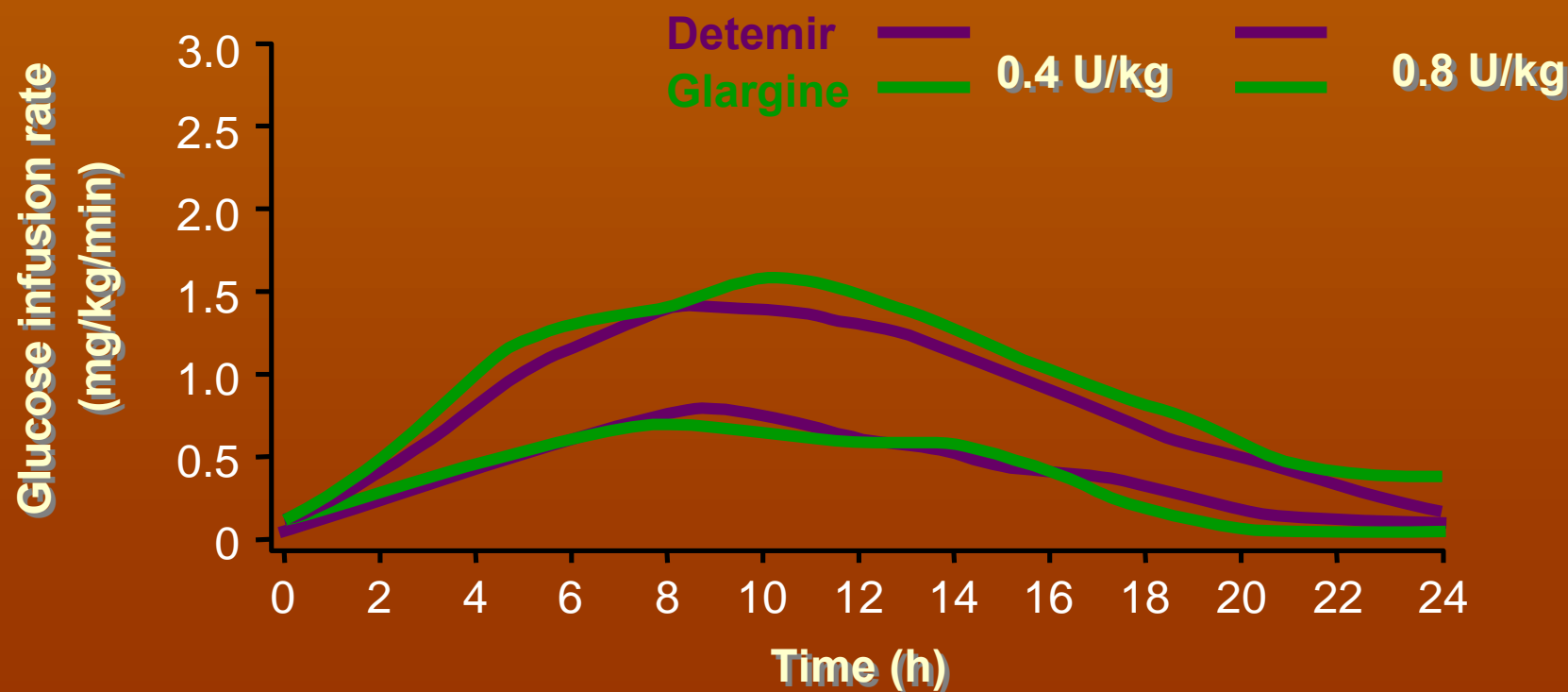
*An additional dose of 1.4 U/kg was tested.
No significant difference in pharmacodynamic was observed.
Klein O, et al. *Diabetes Obes Metab*. 2007;9(3):290-9.

Recommendations for Starting and Adjusting Basal Insulin
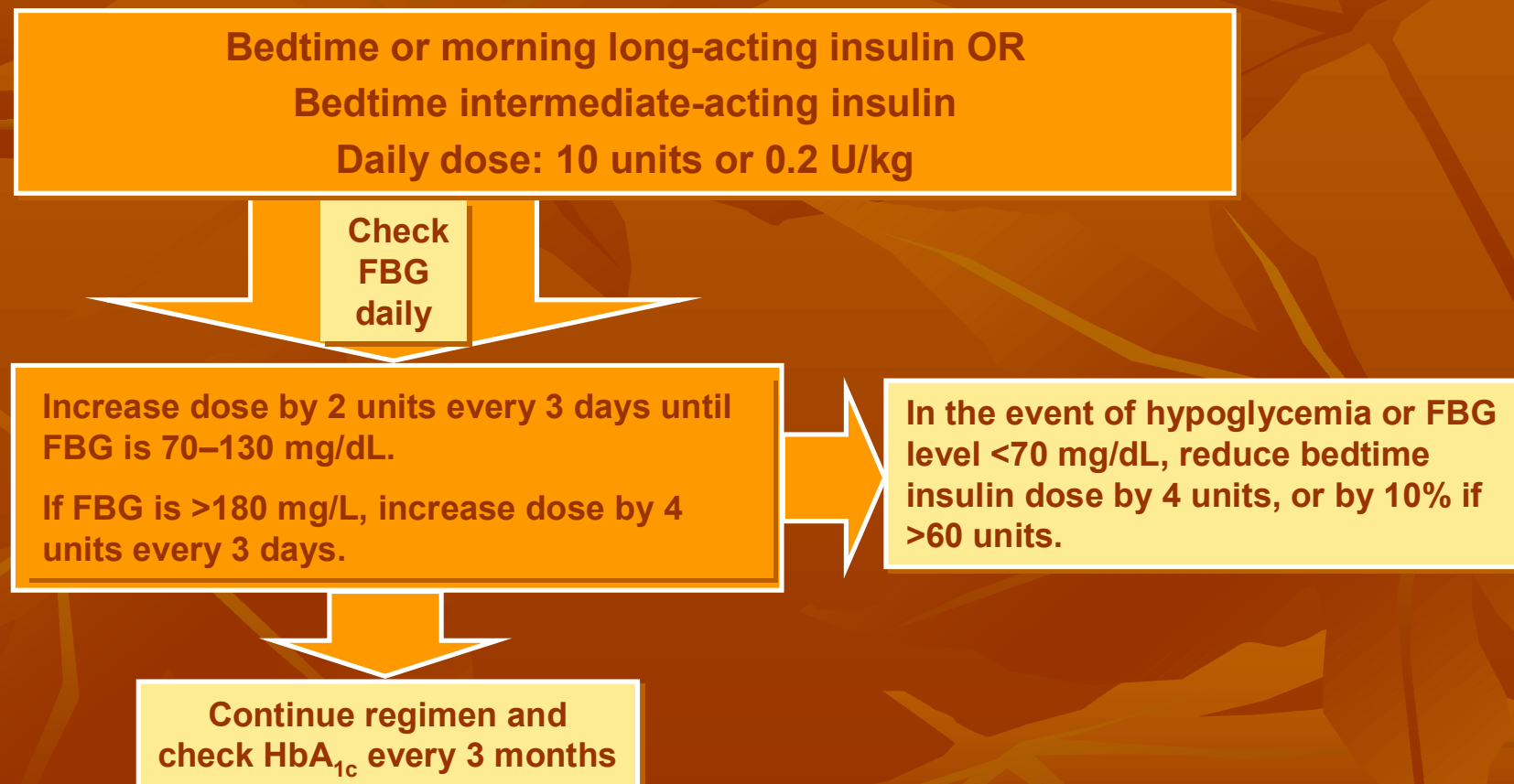
Bedtime or morning long-acting insulin OR

Bedtime intermediate-acting insulin

Daily dose: 10 units or 0.2 U/kg

Check FBG daily

Increase dose by 2 units every 3 days until FBG is 70–130 mg/dL.

If FBG is >180 mg/L, increase dose by 4 units every 3 days.

In the event of hypoglycemia or FBG level <70 mg/dL, reduce bedtime insulin dose by 4 units, or by 10% if >60 units.

Continue regimen and check HbA_{1c} every 3 months

Nathan DM et al. *Diabetes Care* 2009;32:193-203.

John

- 62-yr old male, type 2 diabetes, diagnosed 10 yrs ago
  - BMI 30
- Current therapy:
  - Baby ASA, ACEI, statin
  - Metformin 1g twice a day
  - Glimepiride 4 mg daily
  - Sitagliptin 100mg daily
- Current A1C = 9.4%
- Home glucose ranges
  - FPG = 180-200 mg/dl
  - Pre-supper glucose = 200-250 mg/dL
- ROS positive for polydipsia and nocturia 3 x per night

Start with Basal Insulin
Glargine or Detemir 10 units at bedtime

- Address any misconceptions patient has about insulin - cultural, familial, fear, etc.
- Show patient how to use insulin pen
- Have patient give himself the first injection in the office
- Discuss symptoms and treatment of hypoglycemia
- Provide a self titration schedule
- See the patient in 1-2 weeks

Insulin Pens

- More convenient than traditional vial and syringe
- Repeatedly more accurate dosages
- Easier to use for those with visual or fine motor skills impairments
- Less injection pain
  - Polished and coated needles are not dulled by insertion into a vial of insulin before a second insertion into the skin

John started basal analog insulin 10 units at bedtime

He gave the first injection in the office, using an insulin pen
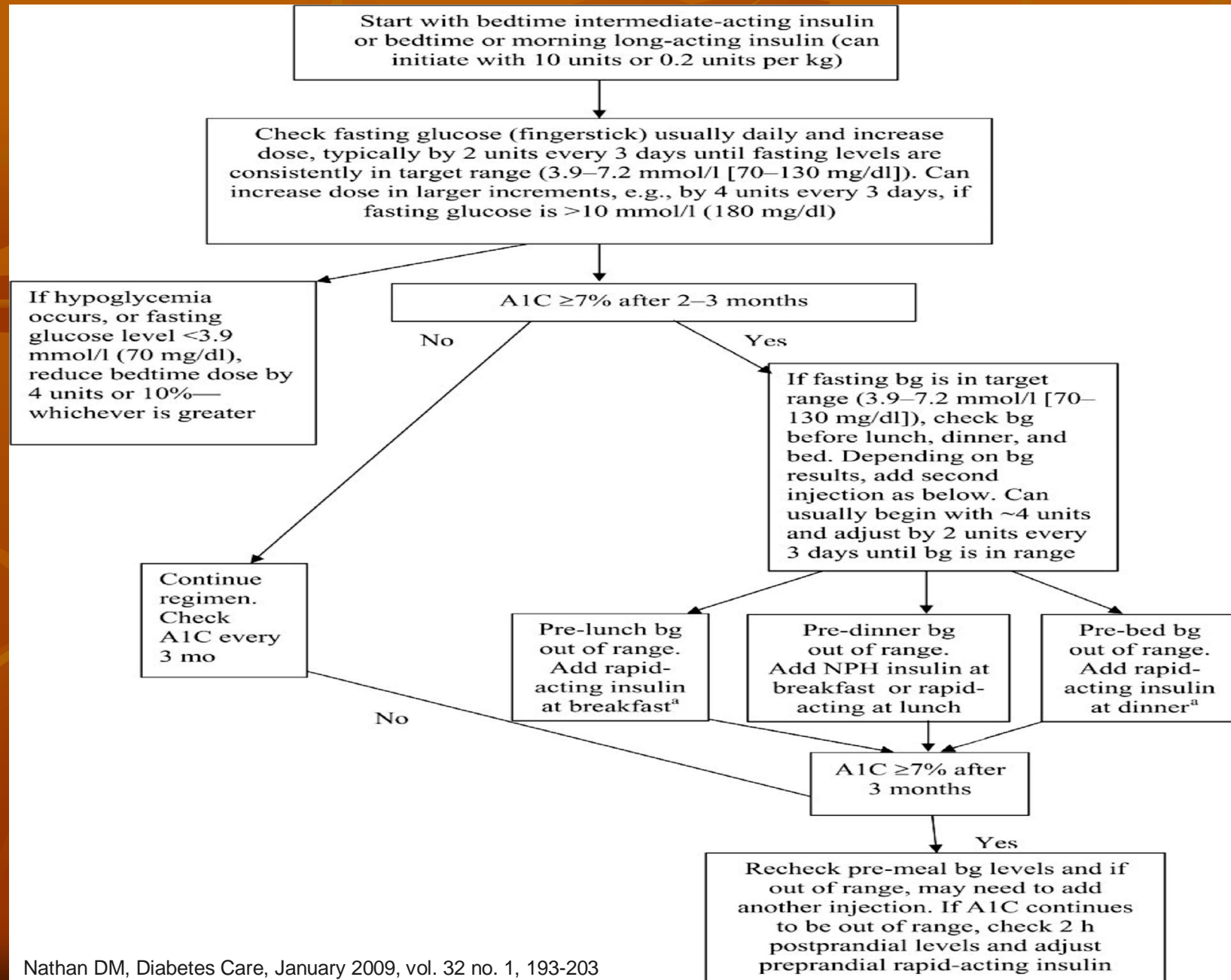
He was provided with a self titration schedule

At 3 month visit:

A1C = 7.9%   FPG = 100-110 mg/dl

ADA Algorithm

Start with bedtime intermediate-acting insulin or bedtime or morning long-acting insulin (can initiate with 10 units or 0.2 units per kg)

Check fasting glucose (fingerstick) usually daily and increase dose, typically by 2 units every 3 days until fasting levels are consistently in target range (3.9–7.2 mmol/l [70–130 mg/dl]). Can increase dose in larger increments, e.g., by 4 units every 3 days, if fasting glucose is >10 mmol/l (180 mg/dl)

If hypoglycemia occurs, or fasting glucose level <3.9 mmol/l (70 mg/dl), reduce bedtime dose by 4 units or 10%— whichever is greater

A1C ≥7% after 2–3 months

No   Yes

If fasting bg is in target range (3.9–7.2 mmol/l [70–130 mg/dl]), check bg before lunch, dinner, and bed. Depending on bg results, add second injection as below. Can usually begin with ~4 units and adjust by 2 units every 3 days until bg is in range

Continue regimen. Check A1C every 3 mo

Pre-lunch bg out of range. Add rapid-acting insulin at breakfast[a]

Pre-dinner bg out of range. Add NPH insulin at breakfast or rapid-acting at lunch

Pre-bed bg out of range. Add rapid-acting insulin at dinner[a]

No

A1C ≥7% after 3 months

Yes

Recheck pre-meal bg levels and if out of range, may need to add another injection. If A1C continues to be out of range, check 2 h postprandial levels and adjust preprandial rapid-acting insulin

Nathan DM, Diabetes Care, January 2009, vol. 32 no. 1, 193-203

Basal Plus Mealtime Insulin

- Start with 1 injection, at meal with the highest post-prandial blood glucoses:
    - 4 units, and titrate,   OR
    - By weight: 0.1 U/kg
- Titrate to:
    - <160 mg/dL 2 hours post-prandial OR
    - <130 mg/dL before next meal or bedtime
- Use rapid-acting analogues, not regular insulin
    - Easier timing, less postprandial hypoglycemia
    - Can be taken up to 20 minutes after start eating

Lispro, Aspart, Glulisine vs Regular Human Insulin
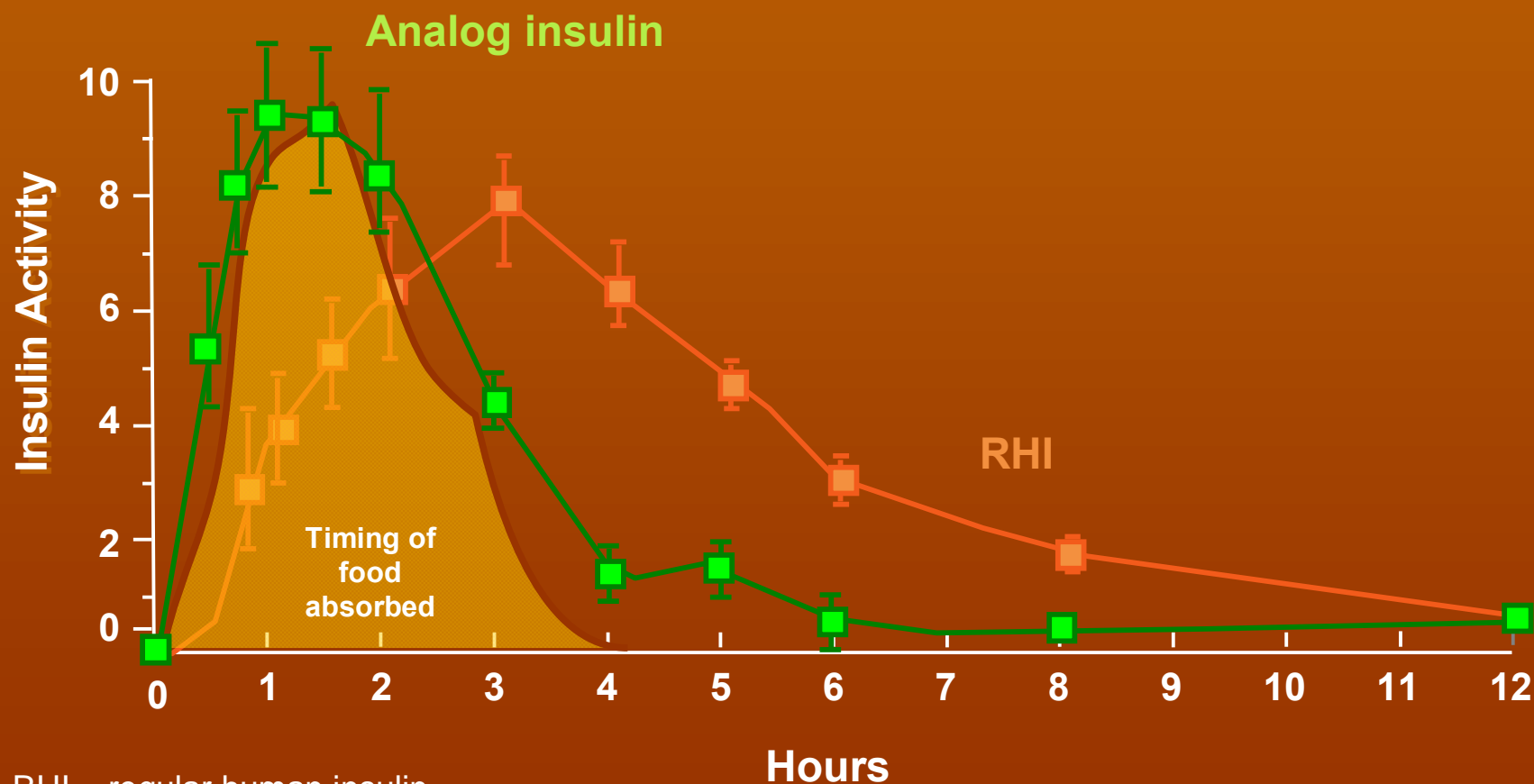
RHI = regular human insulin.

Adapted with permission from Howey DC et al. *Diabetes* 1994;43:396-402.

Basal Plus Two or Three

- If A1c remains $\times$ 7% and FBG and blood glucose levels after meal insulin dose are at target, then

- Add a second dose of pre-meal rapid-acting insulin before the meal that now has the highest post-prandial blood glucoses and titrate until at goal

- Add a third dose of pre-meal rapid-acting insulin if A1c remains $\times$ 7% and FBG and other post-prandial blood glucoses are at goal

- Decrease or stop oral secretagogues when pre-meal insulin is used at two or three meals
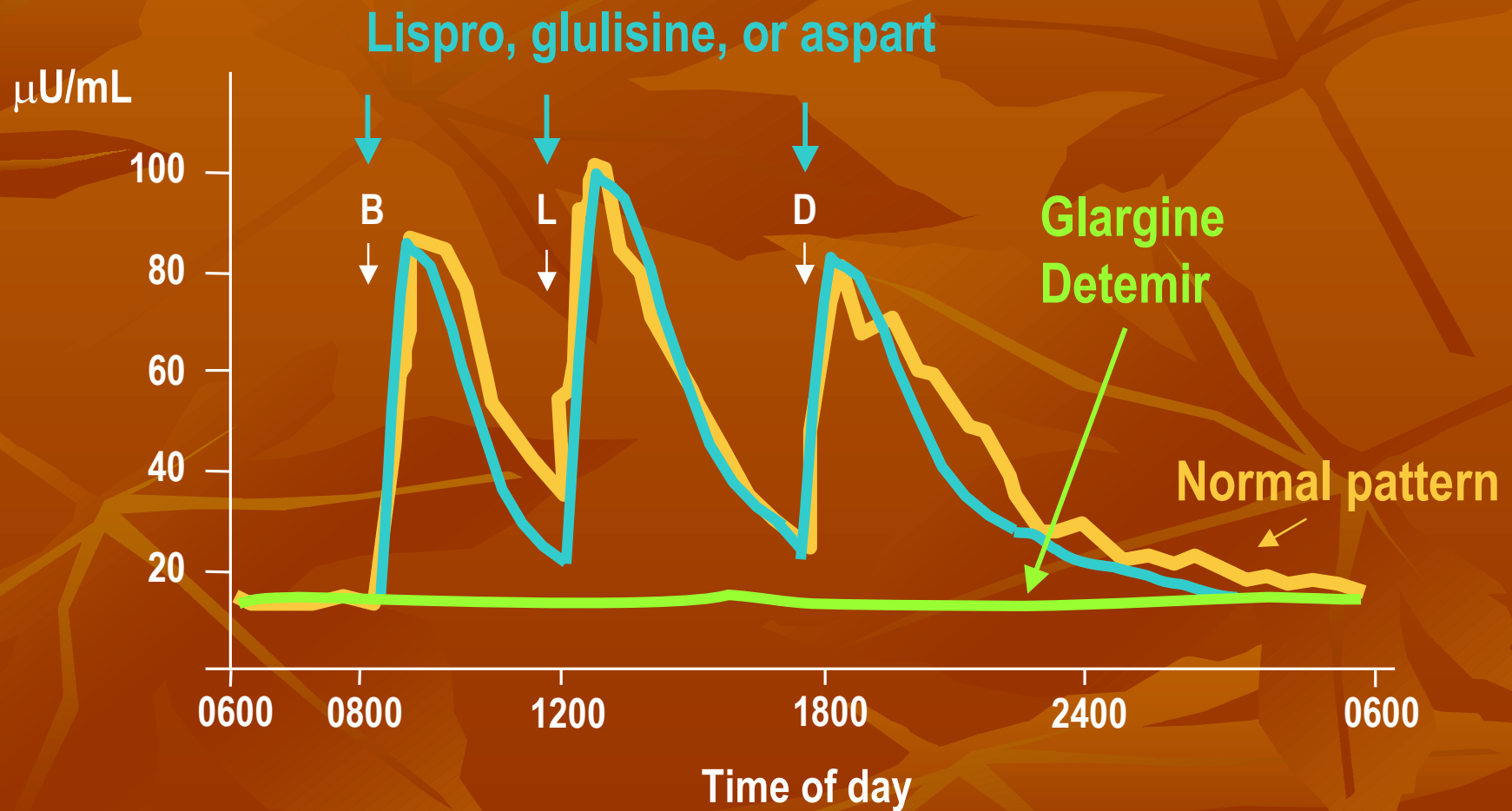
Premixed (Biphasic) Insulin Analogues May Be a Good Choice for Some People . . .

- Those with fairly regular lifestyles, who eat similar amounts at similar times each day and never skip or delay meals

The Basal-Bolus Insulin Concept

- **Basal insulin**
  - Controls glucose production between meals and overnight
  - Nearly constant levels
  - 50% of daily needs
- **Bolus insulin (mealtime or prandial)**
  - Limits hyperglycemia after meals
  - Immediate rise and sharp peak at 1 hour postmeal
  - 10% to 20% of total daily insulin dose at each meal
- **For ideal insulin replacement therapy,** each component should come from a different insulin with a physiologic profile

Basal-Bolus Insulin Treatment With Insulin Analogues

Lispro, glulisine, or aspart

μU/mL

100

B   L   D

80

Glargine
Detemir

60

40

Normal pattern

20

0600   0800   1200   1800   2400   0600

Time of day

B=breakfast; L=lunch; D=dinner

Starting MDI in a 100 kg. person

- Starting Total Daily Dose = 0.5 units/Kg

    TDD= 0.5 x 100 kg. = 50 units

- Basal dose = 50% of TDD once daily

    50% of 50 units = 25 units Basal Insulin daily

- Bolus dose (Meal dose) = 50% of TDD dose divided between meals

    50% of 50 units = 25 units divided by 3 meals

    = 8 units Rapid Insulin with each meal

Give insulin like an endocrinologist

- Use a long-acting basal insulin to cover overnight and between meals
- Use a rapid-acting insulin before meals to cover the CHOøs ingested
- Add correction doses of rapid-acting insulin as needed to correct elevated blood sugars (usually given with scheduled meal-time rapid-acting insulin).
- Note: this is not a sliding-scale

Carb Counting

- Allows for greatest flexibility in lifestyle
- Instruction of patient by CDE or RD in estimation of CHO content of foods
- Provider determines CHO-to-Insulin ratio (CIR)
  - CIR = (2.8 x BWlb)÷TDD   (BWlb = Body Wt in lbs)
- Example for 100 kg person (220 lb)

$$(2.8 \times 220) \div 50 = 12$$

Carb Counting

- Total CHO in meal $\div$ CIR = dose of rapid-acting insulin

- Example: 60 gm CHO meal   CIR 12:1

    $60 \div 12 = 5$ units Rapid-Acting insulin

- If needed, correction bolus given <u>in addition to</u> CHO dose before meal

Correction Bolus (Supplement)

- First determine how much 1 unit of short- or rapid-acting insulin will lower the blood glucose

- This number is known as the correction factor (CF)

- Use the 1700 rule to estimate the CF

- **CF = 1700 divided by total daily dose (TDD)**

  - Ex: if TDD = 50 units,

    then CF = 1700 ÷ 50 = 34

  - Therefore, 1 unit insulin will lower the BG ~34 mg/dl

Correction Bolus Formula

$$\frac{\text{(Current BG - Goal BG)}}{\text{Correction Factor}} = \text{\# units insulin}$$

- Example:
  - Current BG: 220 mg/dl
  - Goal BG: 100 mg/dl
  - Glucose Correction Factor: 34 mg/dl

$$\frac{220 - 100}{34} = 3.5 \text{ units} \quad \text{(round to 4 units)}$$

Pump Technology

Strategies for Overcoming Barriers

- Frame message properly (donøt õblameö patient)
- Discuss real risk of hypoglycemia (low)
- Address cultural taboos and family beliefs
- Fear of weight gain: minimize with diet, exercise
- Starting insulin: get help from CDEs, dietitians, pharmacists; consider group instruction
- Needle phobia: show fine needles, pens
- Convenience: use pens
- Begin therapy with simple regimen: detemir or glargine pen at bedtime

Polonsky W. *Diabetes Educ*. 2007;33(suppl 3):241S. 244S.
Haas L. *Diabetes Educ*. 2007;33(suppl 3):245S. 247S.
Peragallo-Dittko V. *Diabetes Educ*. 2007;33(suppl 3):60S. 65S.

Summary

- Insulin therapy usually needed when A1C is not at goal on multiple anti-diabetic agents
- *In most situations*, first address the fasting blood sugars with basal insulin therapy
  - Monitor blood glucose
  - Adjust other diabetes medication dosages
  - Use adequate insulin doses
- Start pre-meal insulin at the meal with the highest postprandial blood glucose levels
- Promote continued adherence to a healthy diet and regular physical activity
- Be enthusiastic and confident as well as encourage and empower your patients!